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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,077	07/01/2003	Devin Leake	13510CIP	6961

23719 7590 09/07/2005

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EXAMINER

BOWMAN, AMY HUDSON

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/613,077

Applicant(s)

LEAKE ET AL.

Examiner

Amy H. Bowman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 July 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-88 is/are pending in the application.
- 4a) Of the above claim(s) 1-34, 41, 55, 69, 80 and 88 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35-40, 42-54, 56-68, 70-79 and 81-87 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/8/2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/12/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/8/2005, claims 1-88 are pending in the application.

This application contains claims drawn to an invention nonelected with traverse. Specifically, claims 1-34, 41, 55, 69, 80 and 88 have been withdrawn from consideration. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments--Claim Rejections - 35 USC § 102(b)

Claims 75-77, 81 and 83-86 stand rejected under 35 U.S.C. 102(b) as being anticipated by Matulic-Adamic et al. (US 5,998,203), for the reasons of record set forth in the office action mailed 4/12/05.

Applicant argues that Matulic-Adamic et al. does not disclose each and every element of the rejected claims. Applicant asserts that Matulic-Adamic et al. do not

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disclose a double stranded polynucleotide comprising a sense strand, an antisense strand, and a conjugate, wherein the sense and/or antisense strand comprises at least one 2' modified nucleotide. Applicant asserts that the examiner has not indicated where in the Matulic-Adamic et al. reference that the structure of helix 4 in figure 3 is described as comprising a sense and antisense strand and that the examiner has not indicated where Matulic-Adamic et al. disclose a conjugate in combination with the structure of figure 3 or in combination with the structures disclosed in column 3.

Applicant's argument has been considered but is not found persuasive. The description of figure 3 in column 7 of Matulic-Adamic et al. specifically teaches "each N and N' independently is any normal or modified base and each dash represents a potential base pairing interaction. These nucleotides can be modified at the sugar, base, or phosphate." Matulic-Adamic et al. teach a multitude of such modifications in column 3, including 2' modified nucleotides. Matulic-Adamic further teaches "helix 4 can be formed from two separate molecules, i.e. without a connecting loop". Therefore, the structure taught by Matulic-Adamic et al. is a double stranded polynucleotide comprising a sense and antisense strand, wherein the sense and/or the antisense strand comprises at least one 2' modified nucleotide, as instantly claimed. Contrary to applicant's assertion that Matulic-Adamic et al. do not teach a double stranded polynucleotide comprising a sense strand, an antisense strand, and a conjugate, wherein the sense and/or antisense strand comprises at least one 2' modified nucleotide, the structure described above is a double stranded polynucleotide comprising a sense and an antisense strand (see the duplex region) with a 2' modified nucleotide and a conjugate.

Applicant has defined the term "conjugate" to refer to a molecule or moiety that alters the physical properties of a polynucleotide such as those that increase stability and/or facilitate uptake of double stranded RNA by itself (see page 14 of the instant specification). On page 15 of the instant specification, nucleotides or nucleosides are disclosed as example conjugates. Matulic-Adamic et al. teach a multitude of nucleotide conjugates in column 3 that are taught to protect the nucleic acids from exonuclease degradation, resulting in increased half-life of the nucleic acid inside of a cell and improved overall effectiveness of the nucleic acid. The office action mailed 4/12/05 specifically describes the teachings of Matulic-Adamic et al. and refers to figure 3 as an example structure.

Therefore, the 35 U.S.C. 102(b) rejection set forth in the official office action mailed on 4/12/05 is considered proper and maintained.

Claims 75, 76, 78, 79, 81 and 83-86 stand rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550), for the reasons of record set forth in the office action mailed 4/12/05.

Applicant argues that Agrawal et al. does not disclose each and every element of the rejected claims. Applicant asserts that Agrawal et al. discloses oligonucleotides having self-complementary regions for antisense therapeutic approaches as a means of rendering an antisense oligonucleotide resistant to nucleolytic degradation. Applicant asserts that Agrawal et al. do not disclose a double stranded polynucleotide comprising a sense strand, an antisense strand, and a conjugate, wherein the sense and/or the

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antisense strand comprises at least one 2' modified oligonucleotide. Applicant asserts that the rejected claims do not recite each of the stability requirements of Agrawal et al. nor do they require the regions enumerated by Agrawal et al.

Applicant's argument has been considered but is not found persuasive. As stated in the office action mailed 4/12/05, Agrawal et al. teach double-stranded RNA structures wherein the molecules can have modified nucleic acid bases and/or sugars, as well as such molecules having added substituents such as cholesteryl or other lipophilic groups (see page 8). Additionally, Agrawal et al. teaches phosphorothioates, ribonucleotides and 2'-O-methyl modifications (see page 16). Agrawal teaches a double stranded RNA structure with overhangs (see figures 1 and 6). The hairpin structures taught by Agrawal et al. are considered to consist of a sense and an antisense strand in the regions of complementarity between the two. Agrawal et al. teach each and every of the limitations of the instant claims. Contrary to applicant's assertions, it is irrelevant whether the instant claims require the stability requirements or specific regions taught by Agrawal et al. There is well established case law establishing that 102 art can teach additional elements and still be anticipatory. Agrawal et al. teach each of the elements of the instant claims.

Therefore, the 35 U.S.C. 102(b) rejection set forth in the official office action mailed on 4/12/05 is considered proper and maintained.

Response to Arguments--Claim Rejections - 35 USC § 103(a)

Claims 35-40, 42-54, 56-68, 70-79 and 81-87, stand rejected under 35 U.S.C. 103(a), for the reasons of record set forth in the office action mailed 4/12/05.

Applicant states that they disagree with the examiner and traverse each of the obviousness rejections. It is noted that the references have been combined to form one obviousness rejection, so there is only one rejection to traverse. Applicant argues that simply identifying all of the elements in a claim in the prior art does not render a claim obvious. Applicant argues that the rejected claims are not obvious over the prior art because none of the references teach the combination of claimed modifications.

The examiner does not rely on any one reference as teaching the claimed combination of modifications because this is a 35 U.S.C. 103(a) rejection, which is based on the combination of references. If the examiner was relying on one reference to teach each aspect of the claimed invention, the claims would be rejected under 35 U.S.C. 102 rather than 35 U.S.C. 103(a). As exemplified in the office action mailed 4/12/05, the examiner has utilized the prior art to establish that each of the claimed modifications was known in the art at the time the invention was made to add desirable properties to oligonucleotides for delivery. Applicant asserts that the cited references do not suggest the present claims due to the unpredictability in the art regarding certain combinations of modifications. On the contrary, it would merely be routine optimization to determine the specific combinations of modifications to utilize. One would still be motivated to utilize each of the specific modifications claimed, as taught in the cited art, and to optimize the combinations of such modifications. Applicant's arguments rely on

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the fact that there is not one single reference that teaches each aspect of the rejected claims. The examiner has not asserted that this is the case, but rather that the combination of the references teach and render obvious each aspect of the rejected claims. Specifically, applicant asserts that Amarzguioui does not disclose siRNAs comprising at least one orthoester-modified nucleotide, nor siRNAs comprising a lipid conjugate. Amarzguioui was not relied upon for such teachings. The examiner relied upon Scaringe for the teachings of orthoester protecting groups as well as 2' modifications. The examiner relied upon Beigelman for the teachings of lipid conjugates. Applicant further argues that Parrish does not disclose siRNAs comprising at least one orthoester modified nucleotide or siRNAs comprising a lipid conjugate. The examiner did not rely on Parrish for such teachings. The examiner relied upon Scaringe and Beigelman, as explained above. Applicant argues that Beigelman does not disclose double stranded polynucleotides comprising at least one 2' orthoester modification and a conjugate. The examiner did not rely on Beigelman for such teachings. The examiner relied on Beigelman for the teaching of lipid conjugates and their benefits to biologically active compounds including antisense oligonucleotides and siRNA duplexes. Applicant argues that Manoharan does not teach double stranded polynucleotides comprising a sense and an antisense strand and that Letsinger does not teach the claimed invention. The examiner did not rely on these references as teaching the claimed as invention. The examiner relied upon these two references as further evidence that cholesterol is an ideal selection for a lipid conjugate. Regarding motivation, antisense oligonucleotides and siRNA duplexes are both short

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oligonucleotide therapeutics and well known modifications to either one of these compounds would suggest the usage of such modifications in the analogous art to one of ordinary skill in the art. Since each of the modifications were known in the art at the time the invention was made to add beneficial properties to oligonucleotides, one of ordinary skill in the art would have been motivated to utilize each of the instantly claimed modifications or conjugates.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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